REMARKS

Reconsideration of the above-identified application in view of the amendment above and the remarks below is respectfully requested.

No claims have been canceled or added in this paper. Claims 1 and 5 have been amended in this paper. Therefore, claims 1-15 are pending. Of these claims, claims 12-15 are withdrawn as being directed at a non-elected invention, as discussed further below. Accordingly, claims 1-11 are under active consideration.

Claims 1-11 appear to be rejected under 35 U.S.C. 112, second paragraph, as the Patent Office states the following:

> Claims 1-11 are indefinite because they recite a "desired" number of times. It is unclear the metes and bounds of a "desired" number of times. It is unclear if the desired number of times requires the amplification product to be detectable, the amplification product to be enough for another assay, is 1 time enough, is 100 times enough?
>
> Claims 1-11 are indefinite because they recite to reach a "desired" number of nucleic acids. It is unclear if the desired number of nucleic acids refers to a concentration of amplification products, a number of nucleotides incorporated, etc. The metes and bounds of a "desired number of nucleic acids" is unclear.
>
> Claim 1 recites the limitation "the double strand" in step d. There is insufficient antecedent basis for this limitation in the claim.
>
> Claim 5 recites the limitation "the methyl group". There is insufficient antecedent basis for this limitation in the claim.

Without acquiescing in the propriety of the rejection, Applicant has amended claims 1 and 5 so that the language in question is no longer recited.

Accordingly, for at least the above reasons, claims 1-11 are definite, and the subject rejection should be withdrawn.

Claims 1-6, 9 and 10 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010)." In support of the rejection, the Patent Office states the following:

> Genomic methylation pattern is interpreted to include tissue specific methylation patterns.
>
> Lopez et al teaches the amplification of genomic DNA by PCR in the presence of a thermostable DNA methyltransferase (see figure 1 and page 17, lines 26-28) (claim 1) and amplification by single strand displacement amplification and methylation with a DNA methyltransferase (see page 18, line 10-16) for detection. PCR and single strand displacement amplification are interpreted as steps A-C of claim 1. Lopez teaches ^{3}H-s-adenosyl methionine as a methyl donor with a detectable label (see page 4, line 2) (claim 4 and 5). Lopez et al further teaches the use of anchored PCR primers on a solid matrix to create ordered maps (see page 21 lines 2-4) (claim 6). Lopez et al teaches the treatment of amplified targets with a restriction enzyme capable of distinguishing methylated and non-methylated cytosines (see page 32, lines 25-29).
>
> Lopez et al does not teach the use of DNA methyltransferase that preserves methylation status of genomic DNA (claim 1). Lopez et al does not teach the use of DNMT1 a maintenance methyltransferase (claims 2 and 3).
>
> However, Pradhan et al teaches the use of DNMT1 as a methyltransferase (see abstract). Pradhan teaches maintenance methylation "ensures propagation of tissue specific methylation patterns during development" (see page 33002, first column text, lines 8-10). Pradhan thus teaches DNMT1 is a maintenance methyltransferase ensures propagation of specific methylation patterns. Pradhan further teaches cytosine methylation is important in embryonic development, carcinogenesis and genetic disease (see page 33002, 1st column of text lines 1-5). Pradhan thus teaches maintenance methylation and the methyltransferases that maintain methylation patterns are important in embryonic development, carcinogenesis and genetic disease.

> Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the DNMT1 methyltransferase taught by Pradhan as the methyltransferase in Lopez's method because Pradhan teaches DNMT1 is a maintenance methyltransferase that ensures propagation of methylation patterns. The ordinary artisan would be motivated to use the DNMT1 of Pradhan with Lopez method of methylating amplified DNA because Pradhan maintenance methylation are the methyltransferases that maintain methylation patterns are important in embryonic development, carcinogenesis and genetic disease.

Applicant respectfully traverses the subject rejection.

A person of ordinary skill in the art would not have been motivated to substitute the use of a DNA Mtase as taught by Lopez for the BNMT1 enzyme as taught by Pradhan because such a substitution would have rendered the method of Lopez unsuitable for its intended purpose, namely, that of identifying sequence variants within DNA. The use of DNA Mtase enzymes is integral to the functioning of such a method, as such enzymes comprise a sequence specific recognition site. Methyltransferase enzymes, such as DNMT1, do not differentiate DNA molecules on the basis of their sequence. Accordingly, such a substitution would render the method of Lopez unsatisfactory for its intended purpose of identifying DNA sequence variations. Consequently, it is submitted that there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Furthermore, the mere fact that Lopez and Pradhan may be combined does not mean that these references teach or suggest the desirability of combining said references. The Examiner states that "[t]he ordinary artisan would be motivated to use the DNMT1 of Pradhan with Lopez method of methylating amplified DNA because Pradhan maintenance methylation and the methyltransferases that maintain methylation patterns are important in embryonic development, carcinogensis and genetic disease." However, these references do not teach or suggest the desirability of propagating

methylation patterns other than to cite that they are important in embryonic development, carcinogenesis and genetic disease. It is not obvious how such a combination of features from these references would be utilized in the investigation of said biological processes as they do not, by themselves, enable the identification of mutated positions, or variably methylated positions identified therewith. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). A value of the present invention is that it increases the accuracy of methylation assays (such as the use of the bisulfite technique or restriction assays) carried out upon a sample. As PCR is carried out as part of such assays, the desirability of performing a pre-assay methylation retaining amplification step is not immediately apparent.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claim 7 stands rejected under 35 U.S.C. 103(a) "as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claim 1 above, and further in view of Shatkin et al (US Patent 6312926)."

Applicant respectfully traverses the subject rejection. Claim 7 depends from claim 1. Claim 1 is patentable over the combination of Lopez et al. and Pradhan et al. for at least the reasons given above. Shatkin et al. fails to cure all of the deficiencies of Lopez et al. and Pradhan et al. with respect to claim 1. Therefore, based at least on its dependency from claim 1, claim 7 is patentable over the applied combination of Lopez et al., Pradhan et al. and Shatkin et al.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claim 8 stands rejected under 35 U.S.C. 103(a) "as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274,

pages 33002-33010) as applied to claim 1 above, and further in view of Stemple et al (WO/2000/53805)."

Applicant respectfully traverses the subject rejection. Claim 8 depends from claim 1. Claim 1 is patentable over the combination of Lopez et al. and Pradhan et al. for at least the reasons given above. Stemple et al. fails to cure all of the deficiencies of Lopez et al. and Pradhan et al. with respect to claim 1. Therefore, based at least on its dependency from claim 1, claim 8 is patentable over the applied combination of Lopez et al., Pradhan et al. and Stemple et al.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claim 11 stands rejected under 35 U.S.C. 103(a) "as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) as applied to claim 1 and 9 above, and further in view of Gonzalgo et al (US Patent 6251594)."

Applicant respectfully traverses the subject rejection. Claim 11 depends from claim 1. Claim 1 is patentable over the combination of Lopez et al. and Pradhan et al. for at least the reasons given above. Gonzalgo et al. fails to cure all of the deficiencies of Lopez et al. and Pradhan et al. with respect to claim 1. Therefore, based at least on its dependency from claim 1, claim 11 is patentable over the applied combination of Lopez et al., Pradhan et al. and Gonzalgo et al.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-5 stand provisionally rejected "on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-12, 19, 23, and 24 of copending Application No. 10509145."

Applicant respectfully traverses the subject provisional rejection. The subject provisional rejection is based on USSN 10/509,145; however, USSN 10/509,145 is no longer pending. Accordingly, the subject provisional rejection is moot and should be withdrawn.

It is respectfully submitted that the present application is in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Kriegsman & Kriegsman

By: _____

Edward M. Kriegsman
Reg. No. 33,529
30 Turnpike Road, Suite 9
Southborough, MA 01772
(508) 481-3500

Dated: May 29, 2007

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on May 29, 2007.

_____

Edward M. Kriegsman
Reg. No. 33,529
Dated: May 29, 2007